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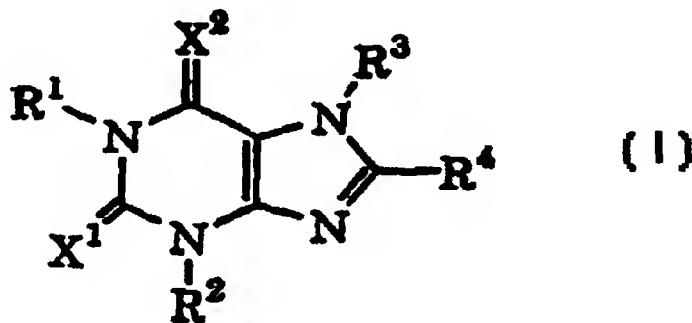
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(54) REMEDIAL AGENT FOR NEURAL DEGENERATION

(57) A remedy for neural degeneration which contains a xanthine derivative represented by general formula (I) or a pharmacologically acceptable salt thereof as the active ingredient.



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DescriptionField of the Invention

5 [0001] The present invention relates to a therapeutic agent for neurodegenerative disorders.

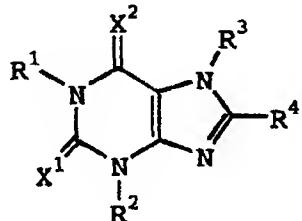
Background of the Invention

10 [0002] Most of the compounds according to the present invention are known compounds, and their adenosine A₂-receptor antagonism, anti-Parkinson's disease action, anti-depressive action, anti-asthmatic action, inhibitory action on bone absorption and action on central excitation are known [Japanese Published Examined Patent Application No. 26516/72, J. Med. Chem., 34, 1431 (1991), J. Med. Chem., 36, 1333 (1993), WO 92/06976, Japanese Published Unexamined Patent Application No. 211856/94, Japanese Published Unexamined Patent Application No. 239862/94, WO 95/23165, Japanese Published Unexamined Patent Application No. 16559/94 and WO 94/01114].

15 [0003] However, it is not known that said compounds have an inhibitory action on neurodegeneration.

Disclosure of the Invention

20 [0004] The present invention relates to a therapeutic agent for neurodegenerative disorders, comprising, as an active ingredient, xanthine derivatives represented by formula (I):



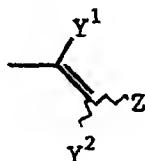
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wherein R¹, R² and R³ independently represent hydrogen, lower alkyl, lower alkenyl or lower alkynyl; R⁴ represents cycloalkyl, -(CH₂)_n-R⁵ (wherein R⁵ represents substituted or unsubstituted aryl, or a substituted or unsubstituted heterocyclic group, and n is an integer of 0 to 4), or the following group:

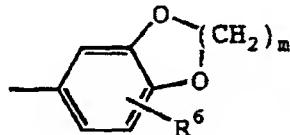
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45 wherein Y¹ and Y² independently represent hydrogen, halogen or lower alkyl, and Z represents substituted or unsubstituted aryl, the following group:

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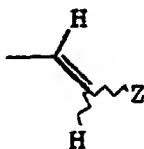


55 (wherein R⁶ represents hydrogen, hydroxy, lower alkyl, lower alkoxy, halogen, nitro or amino, and m is an integer of 1 to 3), or a substituted or unsubstituted heterocyclic group; and X¹ and X² independently represent O or S, or pharmaceutically acceptable salts thereof.

[0005] As the active ingredient for the therapeutic agent for neurodegenerative disorders, preferred compounds are

compounds of formula (I) wherein X¹ and X² are O, or pharmaceutically acceptable salts thereof; or compounds of formula (I) wherein R⁴ is the following group:

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wherein Z has the same meaning as defined above, or pharmaceutically acceptable salts thereof, and specifically preferred compounds are compounds of formula (I) wherein X¹ and X² are O and R⁴ is the group defined above, or pharmaceutically acceptable salts thereof.

15 [0006] Further, the present invention relates to a method of treating neurodegenerative disorders, which comprises administering an effective dose of a xanthine derivative represented by formula (I) or a pharmaceutically acceptable salt thereof.

[0007] Furthermore, the present invention relates to use of a xanthine derivative represented by formula (I) or a pharmaceutically acceptable salt thereof for manufacturing a pharmaceutical composition useful for treatment of neurodegenerative disorders.

20 [0008] Hereinafter, the compound represented by formula (I) is referred to as compound (I).

[0009] In the definition of compound (I), the lower alkyl and the lower alkyl moiety in the lower alkoxy mean a straight-chain or branched C₁ to C₆ alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl and hexyl; the lower alkenyl means a straight-chain or branched C₂ to C₆ alkenyl group such as vinyl, allyl, methacryl, crotyl, 3-butenyl, 2-pentenyl, 4-pentenyl, 2-hexenyl and 5-hexenyl; the lower alkynyl means a straight-chain or branched C₂ to C₆ alkynyl group such as ethynyl, propargyl, 2-butynyl, 3-butynyl, 2-pentylnyl, 4-pentylnyl, 2-hexynyl, 5-hexynyl and 4-methyl-2-pentylnyl; the aryl means phenyl or naphthyl; the cycloalkyl means a C₃ to C₈ cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl; examples of the heterocyclic group are furyl, thienyl, pyrrolyl, pyranyl, thiopyranyl, pyridyl, thiazolyl, imidazolyl, pyrimidyl, triazinyl, 30 indolyl, quinolyl, purinyl and benzothiazolyl; and the halogen includes fluorine, chlorine, bromine and iodine. The substituted aryl and the substituted heterocyclic group have 1 to 3 independently-selected substituents such as lower alkyl, hydroxy, substituted or unsubstituted lower alkoxy, halogen, nitro, amino, lower alkylamino, di(lower alkyl)amino, trifluoromethyl, trifluoromethoxy, benzyloxy, phenyl, phenoxy, lower alkanoyl, lower alkanoyloxy, aroyloxy, aralkanoyloxy, carboxy, lower alkoxy carbonyl, lower alkylcarbamoyl, di(lower alkyl)-carbamoyl, sulfo, lower alkoxy sulfonyl, lower alkylsulfamoyl and di(lower alkyl)sulfamoyl. The lower alkyl and the alkyl moiety of the lower alkoxy, lower alkylamino, di(lower alkyl)amino, lower alkanoyl, lower alkanoyloxy, lower alkoxy carbonyl, lower alkylcarbamoyl, di(lower alkyl)-carbamoyl, lower alkoxy sulfonyl, lower alkylsulfamoyl and di(lower alkyl)sulfamoyl have the same meaning as the lower alkyl defined above. The halogen has the same meaning as the halogen defined above. Examples of the substituents for the substituted lower alkoxy are hydroxy, lower alkoxy, halogen, amino, azido, carboxy and lower alkoxy carbonyl. The 40 alkyl moiety of the lower alkoxy and lower alkoxy carbonyl has the same meaning as the lower alkyl defined above, and the halogen has the same meaning as the halogen defined above. The aroyl moiety of the aroyloxy includes benzoyl and naphthoyl. The aralkyl moiety of the aralkanoyloxy includes benzyl and phenethyl.

[0010] The pharmaceutically acceptable salts of compound (I) include pharmaceutically acceptable acid addition salts, metal salts, ammonium salts, organic amine addition salts and amino acid addition salts.

45 [0011] The pharmaceutically acceptable acid addition salts of compound (I) include inorganic acid addition salts such as hydrochloride, sulfate and phosphate, and organic acid addition salts such as acetate, maleate, fumarate, tartrate, citrate and methanesulfonate; the pharmaceutically acceptable metal salts include alkali metal salts such as sodium salt and potassium salt, alkaline earth metal salts such as magnesium salt and calcium salt, aluminum salt, and zinc salt; the pharmaceutically acceptable ammonium salts include ammonium and tetramethylammonium; the pharmaceutically acceptable organic amine addition salts include salts with morpholine and piperidine; and the pharmaceutically acceptable amino acid addition salts include salts with lysine, glycine and phenylalanine.

50 [0012] Compound (I) including a novel compound can be produced by the methods disclosed in the above-mentioned publications or according to the methods. The desired compound in the process can be isolated and purified by purification methods conventionally used in synthetic organic chemistry, such as filtration, extraction, washing, drying, concentration, recrystallization and various kinds of chromatography.

55 [0013] In the case where a salt of compound (I) is desired and it is produced in the form of a desired salt, it may be subjected to purification as such. In the case where compound (I) is produced in the free form and its salt is desired, it is dissolved or suspended in a suitable solvent, and then an acid or a base may be added thereto to form the salt.

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[0014] Compound (I) and pharmaceutically acceptable salts thereof may be in the form of adducts with water or various solvents, which can satisfactorily be used as the therapeutic agent of the present invention.

[0015] Some of compounds (I) have optical isomers, and all potential stereoisomers and mixtures thereof can satisfactorily be used as the therapeutic agent of the present invention.

5 [0016] Examples of compound (I) are shown in Table 1.

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Table 1

	Compound No.	
5	1	
10	2	
15	3	
20	4	
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30		
35		

Compound 1: (E)-1,3-diethyl-8-(3,4-dimethoxystyryl)-7-methylxanthine (Japanese Published Unexamined Patent Application No. 211856/94)

Melting point: 190.4-191.3 °C

Elemental analysis: C₂₀H₂₄N₄O₄

Calcd. (%): C 62.48, H 6.29, N 14.57

Found (%): C 62.52, H 6.53, N 14.56

IR(KBr) ν_{max} (cm⁻¹): 1697, 1655, 1518

NMR(CDCl₃, 270MHz) δ(ppm): 7.74(1H, d, J=15.5Hz), 7.18(1H, dd,

5 J=8.3, 1.9Hz), 7.08(1H, d, J=1.9Hz), 6.89(1H, d, J=8.3Hz),
 6.77(1H, d, J=15.5Hz), 4.21(2H, q, J=6.9Hz), 4.09(2H, q,
 J=6.9Hz), 4.06(3H, s), 3.96(3H, s), 3.93(3H, s), 1.39(3H, t,
 J=6.9Hz), 1.27(3H, t, J=6.9Hz)

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 15 Compound 2: (E)-8-(3,4-dimethoxystyryl)-1,3-dipropyl-7-methylxanthine (WO 92/06976)

Melting point: 164.8-166.2 °C (Recrystallization from 2-propanol/water)

20 Elemental analysis: C₂₂H₂₈N₄O₄

Calcd. (%): C 64.06, H 6.84, N 13.58

Found (%): C 64.06, H 6.82, N 13.80

25 IR(KBr) v_{max}(cm⁻¹): 1692, 1657

30 NMR(DMSO-d₆, 270MHz) δ(ppm): 7.60(1H, d, J=15.8Hz), 7.04(1H, d, J=2.0Hz), 7.28(1H, dd, J=2.0, 8.4Hz), 7.18(1H, d, J=15.8Hz), 6.99(1H, d, J=8.4Hz), 4.02(3H, s), 3.99(2H, t), 3.90-3.80(2H, m), 3.85(3H, s), 3.80(3H, s), 1.85-1.50(4H, m), 1.00-0.85(6H, m)

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 40 Compound 3: (E)-1,3-diethyl-8-(3-methoxy-4,5-methylenedioxystyryl)-7-methylxanthine (Japanese Published Unexamined Patent Application No. 211856/94)

45 Melting point: 201.5-202.3 °C

Elemental analysis: C₂₀H₂₂N₄O₅

Calcd. (%): C 60.29, H 5.57, N 14.06

50 Found (%): C 60.18, H 5.72, N 13.98

IR(KBr) v_{max}(cm⁻¹): 1694, 1650, 1543, 1512, 1433

5 NMR(DMSO-d₆, 270MHz) δ(ppm): 7.58(1H, d, J=15.8Hz), 7.23(1H,
 10 d, J=15.8Hz), 7.20(1H, d, J=1.0Hz), 7.09(1H, d, J=1.0Hz),
 15 6.05(2H, s), 4.09-4.02(2H, m), 4.02(3H, s), 3.94-3.89(2H, m),
 20 3.89(3H, s), 1.25(3H, t, J=7.2Hz), 1.13(3H, t, J=6.9Hz)

10 Compound 4: (E)-8-(3,4,5-trimethoxystyryl)caffeine (Japanese
 15 Published Examined Patent Application No. 26516/72)

15 IR(KBr) νmax(cm⁻¹): 1702, 1667, 1508, 1432
 20 NMR(DMSO-d₆, 270MHz) δ(ppm): 7.61(1H, d, J=16.0Hz), 7.25(1H,
 25 d, J=16.0Hz), 7.09(2H, s), 4.03(3H, s), 3.85(6H, s), 3.71(3H,
 30 s), 3.45(3H, s), 3.21(3H, s)
 35 MS(EI) 386(M⁺)

25 [0017] Hereinafter, the pharmacological activity of compound (I) is shown by the following Test Examples.

30 Test Example 1: Inhibitory Action on Neurodegeneration

- 35 [0018] The experiment was conducted according to the method of Sundstrom et al. (Brain. Res. Bulletin, 21, 257-263 (1988)).
 40 [0019] In the experiment, 9- to 10-week-old male C57BL/6NCrj mice (supplied by Nippon Charles River) were used. During the period of preliminary breeding, the animals were kept in a laboratory at room temperature (22 to 24 °C) under 50 to 60 % humidity and allowed food and water ad libitum.
 45 [0020] 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride (abbreviated hereinafter as MPTP HCl (RBI Co., Ltd.)) was dissolved at a concentration of 4 mg/ml in physiological saline. A test compound was suspended at a concentration of 1 mg/ml in 0.3 % dimethyl sulfoxide (DMSO). Each test group consisted of 9 to 10 animals, and a control group was intraperitoneally given physiological saline, and an MPTP HCl administration group and an MPTP HCl + test compound administration group were intraperitoneally given MPTP HCl (40 mg/kg).
 50 [0021] After 1 hour, the control group and the MPTP HCl administration group were orally given 0.3 % Tween, and the MPTP HCl + test compound administration group was orally given the test compound (10 mg/kg). After 1 week, the animals were decapitated, and the striatum was removed therefrom under cooling on ice. The striatum was stored in a deep freezer (< -80°C) before a binding experiment.
 55 [0022] A [³H]-mazindol binding test was conducted in the following method. A striatum and 300 μl of buffer (120 mM NaCl, 5 mM KCl, 50 mM Tris, pH 7.9) were put into a micro-centrifuge tube and homogenized by portable homogenizer S-203 (manufactured by Ikeda Rika) and centrifuged at 15,000 rpm, 4°C for 5 minutes (by KUBOTA 1710). The precipitates were suspended in 300 μl of buffer and then centrifuged again at 15,000 rpm, 4°C for 5 minutes. The precipitates were suspended in 500 μl of buffer and then distributed into four test tubes in 100 μl portions. The remaining suspension (100 μl) was used for protein quantification. To determine non-specific binding, nomifensine maleate (RBI Co., Ltd.) (final concentration: 10 μM) as an inhibitor of dopamine uptake was added to two test tubes among the four test tubes. The binding reaction was initiated by adding 25 μl of [³H]-mazindol (final concentration: 10 nM) (Spec. Act. 888 GBq/mmol, a product of NET). The mixture was incubated for 1 hour under cooling on ice, and the striatum homogenate was adsorbed onto a glass filter (Whatman, GF/B) in a cell harvester and washed three times with 5 ml of buffer. The radioactivity on the glass filter was measured with a liquid scintillation counter. For each striatum, specific [³H]-mazindol binding was determined by subtracting the average of non-specific [³H]-mazindol binding from the average of total [³H]-mazindol binding.
 60 [0023] Protein quantification was conducted by use of a Bio-Rad DC protein assay kit (Bio-Rad Co., Ltd.) with

bovine serum albumin (Sigma Co., Ltd.) as a standard. Specific [³H]-mazindol binding was expressed as the amount of bound [³H]-mazindol per unit weight of protein, and the mean ± standard error was determined for each group (10 animals).

[0024] In Table 2, the results are expressed in terms of the amount of specifically bound [³H]-mazindol (fmol/mg protein) in the striatum.

Table 2

Test groups	
Control	1140.3±50.0
MPTP HCl	616.3±32.8###
MPTP HCl + compound 1	950.9±54.1***
Control	1219.3±66.4
MPTP HCl	621.2±27.7###
MPTP HCl + compound 2	784.8±41.6**
MPTP HCl + compound 3	794.9±28.5**
Control	1214.8±46.2
MPTP HCl	674.2±38.1###
MPTP HCl + compound 4	923.5±51.1**

**: p < 0.01 (compared with the group given

MPTP HCl alone).

***: p < 0.001 (compared with the group given
MPTP HCl alone).

###: p < 0.001 (compared with the control
group).

(n = 9 to 10; Wilcoxon rank sum test)

[0025] According to the test results, the reduction of the amount of specifically bound [³H]-mazindol by administration of MPTP HCl was inhibited by compound 1. That is, it was revealed that compound 1 exhibits inhibitory action on degeneration of dopaminergic neurons.

Test Example 2: Acute Toxicity Test

[0026] Test compounds were orally or intraperitoneally administered to groups of dd-strain male mice weighing 20 ± 1 g, each group consisting of three mice. Seven days after the administration, the mortality was observed to determine a minimum lethal dose (MLD) of each compound.

[0027] The MLD value of Compound 1 was greater than 1000 mg/kg for oral administration.

[0028] Compound (I) or pharmaceutically acceptable salts thereof have inhibitory action on neurodegeneration and are useful as a therapeutic agent for neurodegenerative disorders such as Alzheimer's disease, progressive supranuclear palsy, AIDS brain fever, propagating spongy brain fever, Huntington's chorea, multiple sclerosis, amyotrophic lateral sclerosis (ALS), multi-system atrophy, brain ischemia, and attention deficit hyperactivity disorder.

[0029] Compound (I) or pharmaceutically acceptable salts thereof can be used as such or in the form of various pharmaceutical compositions. The pharmaceutical compositions of the present invention can be prepared by uniformly mixing an effective amount of compound (I) or a pharmaceutically acceptable salt thereof as an active ingredient with pharmaceutically acceptable carriers. The pharmaceutical compositions are preferably in a unit dosage form suitable for rectal administration, oral or parenteral (including subcutaneous, intravenous and intramuscular administration) administration, etc.

[0030] For preparing a pharmaceutical composition for oral administration, any useful pharmaceutically acceptable carriers can be used. For example, liquid preparations for oral administration such as suspension and syrup can be prepared using water; sugars such as sucrose, sorbitol and fructose; glycols such as polyethylene glycol and propylene glycol; oils such as sesame oil, olive oil and soybean oil; preservatives such as a p-hydroxybenzoate; flavors such as strawberry flavor and peppermint, etc. Powder, pills, capsules and tablets can be prepared using excipients such as lactose, glucose, sucrose and mannitol; disintegrating agents such as starch and sodium alginate; lubricants such as mag-

nesium stearate and talc; binders such as polyvinyl alcohol, hydroxypropyl cellulose and gelatin; surfactants such as fatty acid esters; plasticizers such as glycerin, etc. Tablets and capsules are the most useful oral unit dosage because of the readiness of administration. For preparing tablets and capsules, solid pharmaceutical carriers are used.

[0031] Injectable preparations can be prepared using carriers such as distilled water, a salt solution, a glucose solution and a mixture of a salt solution and a glucose solution. The preparation can be prepared in the form of solution, suspension or dispersion according to a conventional method by using a suitable auxiliary.

[0032] Compound (I) or a pharmaceutically acceptable salt thereof can be administered orally in the pharmaceutical form described above or parenterally as the injection. The effective dose and administration schedule vary depending on the mode of administration, age, weight, and symptoms of a patient, etc. However, generally, compound (I) or a pharmaceutically acceptable salt thereof is administered in a dose of 1 to 900 mg/60 kg/day, preferably in a dose of 1 to 200 mg/60 kg/day.

[0033] Certain embodiments of the present invention are described in the following examples.

EXAMPLE

[0034] Tablets having the following composition were prepared in a conventional manner.

[0035] Compound 1 (40 g) was mixed with 286.8 g of lactose and 60 g of potato starch, followed by addition of 120 g of a 10% aqueous solution of hydroxypropyl cellulose. The resultant mixture was kneaded, granulated, and then dried by a conventional method. The granules were refined to give granules used to make tablets. After mixing the granules with 1.2 g of magnesium stearate, the mixture was formed into tablets each containing 20 mg of the active ingredient by using a tablet maker (Model RT-15, Kikusui) having pestles of 8 mm diameter.

[0036] The prescription is shown in Table 3.

Table 3

Compound 1	20 mg
Lactose	143.4 mg
Potato Starch	30 mg
Hydroxypropyl Cellulose	6 mg
Magnesium Stearate	0.6 mg
	200 mg

Example 2: Capsules

[0037] Capsules having the following composition were prepared in a conventional manner.

[0038] Compound 1 (200 g) was mixed with 995 g of Avicel and 5 g of magnesium stearate. The mixture was put in hard capsules No. 4 each having a capacity of 120 mg by using a capsule filler (Model LZ-64, Zanashi) to give capsules each containing 20 mg of the active ingredient.

[0039] The prescription is shown in Table 4.

Table 4

Compound 1	20 mg
Avicel	99.5 mg
Magnesium Stearate	0.5 mg
	120 mg

Example 3: Injections

[0040] Injections having the following composition were prepared in a conventional manner.

[0041] Compound 1 (1 g) was dissolved in 100 g of purified soybean oil, followed by addition of 12 g of purified egg

yolk lecithin and 25 g of glycerin for injection. The resultant mixture was made up to 1,000 ml with distilled water for injection, thoroughly mixed, and emulsified by a conventional method. The resultant dispersion was subjected to aseptic filtration by using 0.2 µm disposable membrane filters, and then aseptically put into glass vials in 2 ml portions to give injections containing 2 mg of the active ingredient per vial.

- 5 [0042] The prescription is shown in Table 5.

Table 5

10	Compound 1	2 mg
	Purified Soybean Oil	200 mg
15	Purified Egg Yolk Lecithin	24 mg
	Glycerine for Injection	50 mg
	Distilled Water for Injection	1.72 ml
		2.00 ml

Example 4: Anal suppository

20 [0043] Formulations for rectal administration having the following composition were prepared in a conventional manner.

[0044] Witepsol® H15 (678.8 g, manufactured by Dynamit Nobel, Ltd.) and Witepsol® E75 (290.9 g, manufactured by Dynamit Nobel, Ltd.) were melted at 40 to 50 °C. In the resulting molten mixture were uniformly mixed and dispersed 25 Compound 1 (2.5 g), potassium dihydrogen phosphate (13.6 g) and disodium hydrogen phosphate (14.2 g). The resulting dispersion was poured into plastic suppository molds, and gradually cooled to give anal suppositories containing 2.5 mg of the active ingredient per formulation.

[0045] The prescription is shown in Table 6.

Table 6

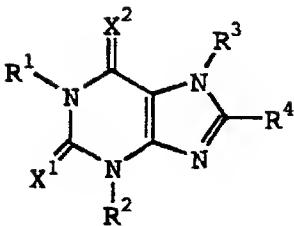
30	Compound 1	2.5 mg
	Witepsol H15	678.8 mg
35	Witepsol E75	290.9 mg
	Potassium dihydrogen phosphate	13.6 mg
	Disodium hydrogen phosphate	14.2 mg
40		1000 mg

Industrial Applicability

[0046] The present invention provides a therapeutic agent for neurodegenerative disorders, comprising a xanthine derivative or a pharmaceutically acceptable salt thereof as an active ingredient.

Claims

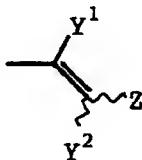
- 50 1. A therapeutic agent for neurodegenerative disorders comprising, as an active ingredient, a xanthine derivative represented by formula (I):



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wherein R¹, R² and R³ independently represent hydrogen, lower alkyl, lower alkenyl or lower alkynyl; R⁴ represents cycloalkyl, -(CH₂)_n-R⁵ (wherein R⁵ represents substituted or unsubstituted aryl, or a substituted or unsubstituted heterocyclic group, and n is an integer of 0 to 4), or the following group:

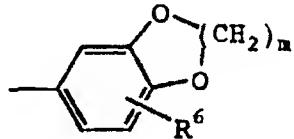
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wherein Y¹ and Y² independently represent hydrogen, halogen or lower alkyl, and Z represents substituted or unsubstituted aryl or the following group:

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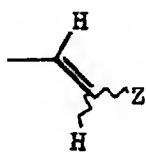
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(wherein R⁶ represents hydrogen, hydroxy, lower alkyl, lower alkoxy, halogen, nitro or amino, and m is an integer of 1 to 3), or a substituted or unsubstituted heterocyclic group; and X¹ and X² independently represent O or S, or a pharmaceutically acceptable salt thereof.

40

2. The therapeutic agent for neurodegenerative disorders according to claim 1 comprising the compound wherein X¹ and X² are O, or a pharmaceutically acceptable salt thereof as an active ingredient.
3. The therapeutic agent for neurodegenerative disorders according to claim 1 or 2 comprising, as an active ingredient, the compound wherein R⁴ is the following group:

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wherein Z has the same meaning as defined above, or a pharmaceutically acceptable salt thereof.

55

4. A method of treating neurodegenerative disorders, which comprises administering an effective dose of a xanthine derivative according to any one of claims 1 to 3 or a pharmaceutically acceptable salt thereof.
5. Use of a xanthine derivative according to claims 1 to 3 or a pharmaceutically acceptable salt thereof for manufacturing a pharmaceutical composition useful for treatment of neurodegenerative disorders.

INTERNATIONAL SEARCH REPORT		International application No. PCT/JP98/03980
A. CLASSIFICATION OF SUBJECT MATTER Int.Cl' A61K31/52 // C07D473/04, C07D473/20, C07D473/22		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) Int.Cl' A61K31/52, C07D473/04, C07D473/20, C07D473/22		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Caplus (STN), REGISTRY (STN)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP, 2613355, B2 (Kyowa Hakko Kogyo Co., Ltd.), 27 February, 1997 (27. 02. 97) & EP, 590919, A1 & NO, 9303452, A & CA, 2107014, A & US, 5484920, A & US, 5587378, A & BR, 1100971, A3	1-3, 5
X	JP, 2613352, B2 (Kyowa Hakko Kogyo Co., Ltd.), 27 February, 1997 (27. 02. 97) & EP, 565377, A1 & NO, 9301317, A & CA, 2093403, A & US, 5484920, A & US, 5587378, A & DE, 69316067, E & ES, 2112386, T3 & BR, 1100636, A3	1-3, 5
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<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
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Date of the actual completion of the international search 25 November, 1998 (25. 11. 98)		Date of mailing of the international search report 8 December, 1998 (08. 12. 98)
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